MEMORANDUM

DATE: February 24, 2009

TO: OMB-PRA staff

FROM: CDC NCBDDD personnel Reefhuis, Honein, Yowe-Conley, and Campbell

RE: Response to three issues discussed on February 12th regarding 0920-0010: The National Birth Defects Prevention Study

On February 12th at 11:00AM, a conference call was held to discuss 0920-0010. Three specific issues were discussed during the call. *First*, the issue of participants being given access to the results for non-CLIA approved tests. *Second*, the issue of NIH or other government agency collaboration and approval of the CATI items involving the dietary assessment of the participants. *Third*, the issue of the extent of the burden collection thought to be approved by the OMB during past iterations of this data collection activity.

Unfortunately, nobody here at CDC on the call that day had sufficient history with the project to speak with knowledge regarding the origin of these issues. After the call, persons within the Program were sought and answers emerged. Therefore, our response to each issue is below, and we are eager to hold a follow-up conference call to discuss each of these issues. For our next call, we will also have present Dr. Peggy Honein, who has been involved in this project for a number of years and can best speak to the issues below.

Issue #1: Participant access to non-CLIA approved tests

The CDC staff is in complete agreement with the OMB-PRA staff on this issue; it was the original desire of the CDC investigators to NOT provide non-CLIA approved test results to participants. However, the origin for this action was in response to a request made by the previous chairman of one of the CDC IRBs about five years ago. About one year ago, in fact, an independent ethical consultation provided to our staff advised a similar amendment to the protocol accordingly. At that time it was felt that the opinion of a sole ethicist would not provide sufficient leverage to justify the amendment request to the IRB. Now that the OMB office has also rendered its opinion on this subject, an amendment request has already been submitted to the CDC office, stating that three sentences from the consent form regarding access to individual test results be struck from the consent, with the rationale being that:

OMB has requested removal of these sentences since the test results are currently research-based, non-CLIA approved tests, and informing individual participants of individual results regarding experimental tests is outside of standard clinical practice for research protocols, is of questionable value, and may provide participants with misleading information.

We have left intact the current consent form language that states: "For any tests that have clinical importance, we will publish summarized results in the study newsletter. This newsletter is sent to all participants. If you have questions about whether any genetic tests would be useful to you, we recommend that you consult your health care provider." An amended version of the consent form is thus submitted to the OMB as Attachment O.

Issue #2: NIH collaboration on dietary assessment

The input of the National Institutes of Health has been previously sought for this project, most recently in October 2008. Below is recent correspondence from Dr. Amy Subar, PhD, MPH, RD, in regard to this issue:

From: Subar, Amy (NIH/NCI) [E]
To: Reefhuis, Jennita (CDC/CCHP/NCBDDD)
Sent: Mon Feb 23 09:39:57 2009
Subject: National Birth Defects Prevention Study: Collection of dietary information
Dear Jennita,

The purpose of this note is to support the current dietary data collection methods in the National Birth Defects Prevention Study (NBDPS). As part of the "NBDPS Future Directions Workshop" in October, 2008, I was asked to review the questionnaire for NBDPS and determine whether the collection of dietary information could be improved. At that time, I recommended that you not make changes in your dietary data collection instrument.

There are, in fact, other more valid dietary assessment methods such as 24-hour dietary recalls, food records or biological specimens, but they only reflect current intake. In this study it is not possible to use them because of interest in collecting retrospective data before and during pregnancy. For this, recalls, records or specimens would likely not reflect food patterns during the period of interest (Olson et al., 2005; George et al., 2005). Given that this is a study of a rare condition, i.e., birth defects, NBDPS researchers, understandably used a case-control design to collect retrospective data on dietary exposures during crucial periods of embryonic development before and during pregnancy. The only dietary assessment instrument that can be used in a case-control design is a food frequency questionnaire (FFQ). The FFQ used to collect most of the dietary information in NBDPS is a shortened modified Harvard FFQ. Though all FFQs are thought to contain a fair amount of measurement error, the FFQ used in this research has been shown to be as valid as other FFQs in comparison with other self-report methods such as 24 hour dietary recalls and diet records (Maruti et al., 2006; Willett and Lenart, 1998; Fawzi et al., 2004; Subar et al., 2001). The validity of shorter FFQs for ranking individuals according to their nutrient intake also compares well with other methods and is less burdensome for the participant (Willet et al., 1985; Rifas-Shiman et al., 2001). In NBDPS, due to interest in specific nutrients such as folate, additional detailed data is collected on consumption of fortified foods including cereals and beverages. There are other widely used FFQs available for use, but after energy adjustment no one food frequency questionnaire is remarkably better than another for assessment of nutrient intakes (Subar et al., 2001).

As I said at the Workshop, it is my belief that the dietary assessment questionnaire used in NBDPS is one of high quality and comparable to other FFQs in use. Given the overall length of the entire NBDPS questionnaire, the FFQ used is of reasonable length – it collects enough pertinent data without overburdening the subject. In addition, at this point in time, switching methods would eliminate the comparability of data across time. For rare birth defects, switching methods would translate into reduced statistical power to study dietary exposures.

If you have any further questions, please email me at subara@mail.nih.gov or contact me at 301-594-0831.

Sincerely,

Amy F. Subar, PhD, MPH, RD
National Cancer Institute
Division of Cancer Control and Population Sciences
Applied Research Program
Risk Factor Monitoring and Methods Branch
6130 Executive Boulevard
EPN 4005
Bethesda, MD 20892-7344
Phone: 301-594-0831
Fax: 301-435-3710
subara@mail.nih.gov

Issue #3: The estimate of burden in the current and previous versions of this data collection activity.

The initial OMB application and subsequent OMB renewals for the National Birth Defects Prevention Study (NBDPS) conducted by the Centers for Birth Defects Research and Prevention (CBDRP) have consistently described the multi-site nature of the study and specified that all sites were conducting the same computer assisted maternal telephone interview with participants. We have included the specific language from the initial application in 1999 and the 2002 and 2005 renewal applications below. Throughout the course of the study, CDC has provided cooperative agreements to multiple sites to conduct birth defects research which included participation in the NBDPS. And, CDC has maintained a CDC site of the NBDPS throughout this time, with cases and controls ascertained from the five central counties of metropolitan Atlanta.

While all of the sites are described in each OMB application, the burden table in each application has been based only on the CDC site of the NBDPS --- meaning the metropolitan Atlanta site of the study. The original guidance for preparation of the burden table in this manner was provided prior to any of the current staff joining CDC, thus the specifics of this guidance are somewhat unclear. However, it appears that this was because the Atlanta site was the only site with research being directly conducted by CDC.

In preparing the current OMB renewal, we discussed this issue within our center, and decided it was most appropriate to include all participating sites in calculating the estimated burden of the study. Thus, the burden table has changed substantially from previous applications. However, this is not a change in the burden of the study, but rather a change in reporting to include all sites participating in the study under CDC cooperative agreements – in addition to the CDC site. We regret that the discrepancy between the previous narratives and the Burden Statements was NOT described in detail in our current submission, and an explanation as to the fact that we were now intending to ensure that the Burden Estimate correction lined up with the past and present narratives describing the full burden of the project across all participating sites.

Statements/wordings for approved OMB submissions mentioning ALL Centers

1999 OMB Initial Application

Page 6:
In 1997 CDC awarded cooperative agreements to 7 states (AR, CA, IA, MA, NJ, NY, TX) to establish Centers for Birth Defects Research and Prevention (Attachment C). One of the main activities for each Center was to conduct the BDRFS in their state (see section A.4)

Attachment C: List of Centers for Birth Defects Research and Prevention

A.4. – Page 9:
The NBDPS is being conducted by the Centers for Birth Defects Research and Prevention (CBDRP) in seven states (AR, CA, IA, MA, NJ, NY, TX) and by the Division of Birth Defects and Pediatric Genetics, CDC in Atlanta. All of the Centers are using the same processes for identifying eligible cases and controls, participant contact, data collection, and data processing. Collaboration among these Centers and CDC is essential for the success of the NBDPS because

it allows scientists with differing expertise to work together, substantially improving ability to better understand birth defect risk factors. Because birth defects are rare, it takes many years to accumulate enough cases of a particular defect to have the power to study risk factors for that defect. This collaborative effort will enable researchers to study the Epidemiology of some rare birth defects for the first time. It may also enable researchers to identify rare exposures, such as genetic variations, that are associated with the more common birth defects.

Page 8:
The NBDPS is being conducted at 8 locations around the country. To facilitate the compilation of the data, the interview data is sent to CDC via dial-up modem using the Microsoft Access 97 replication feature. The replication process enables the data to be transferred to the central storage database at the same time that the CATI program is updated. Whenever program corrections are made to the CATI, each site receives those changes when they replicate their data. This way, all of the sites are kept standardized.

Page 10. Consulation through other sources:
The principal investigators at each CBDRP work collaboratively with CDC scientists on scientific aspects of study design and analysis, including development of the study protocol, interview instrument design, and study conduct. Committees were formed with representatives from each CBDRP to design the collaborative case-control study. The **standards committee** designed the protocol for the study including standard forms and procedures for identifying, contacting, and interviewing study participants. The **questionnaire committee** revised the BDRFS mother interview instrument and arranged to have the questionnaire placed into a CATI format. The questionnaire committee is also evaluating the current interview instrument. The **clinicians committee** (geneticists and clinicians from each CBDRP) decided on the case definitions for the 30 birth defects included in the study and developed guidelines to assist with case identification and review, medical record abstraction, and coding. The **biologic committee** designed the protocol for the collection of biologic samples and developed a plan for banking, sharing the biologic specimens, is responsible for the ongoing quality control analysis of the biologic samples and the recommendation of genes for study. The **data sharing committee** has the ongoing task of deciding how the data will be equitably shared for analysis purposes. This committee is responsible for review of all protocols for data analysis as well as addressing human subjects issues, data access, collaboration, and authorship. The scientists involved in the NBDPS represent the greatest concentration of expertise and experience on birth defects in the United States (please see **Attachment H** for a detailed list of collaborators).
There have been no major problems identified through these consultations.

A.10. Page 12: Assurance of Confidentiality Provided to the Respondents

The Privacy Act Officer reviewed this OMB application and has determined that the Privacy Act is applicable. A contractor will be used by NCBDDD to conduct interviews for the Atlanta site. Full names of respondents must be collected to enable the study purposes to be achieved. Records will be covered under the CDC Privacy Act system of records 09-20-0136, Epidemiologic Studies and Surveillance of Disease Problems. The NBDPS is based on the previous experience of the BDRFS, which was initiated at CDC and had 308(d) confidentiality assurance protection. The BDRFS was expanded in 1997 through cooperative agreements. The

activities of the NBDPS project are both intramural and extramural, consisting of one CDC operated site in Atlanta, Georgia, and nine CDC-funded cooperative agreements in nine other states. Because all sites (except the CDC's Atlanta site) were funded by cooperative agreements and protection was needed for data at each site, it was determined by the CDC Office of General Counsel and the CDC Confidentiality Officer that a 301(d) Certificate of Confidentiality was the appropriate confidentiality protection. NBDPS received a Certificate of Confidentiality for the eight original study sites in August 1999.

2002 OMB Renewal Application

Page 7-8:
In 1997 CDC awarded cooperative agreements to 7 states (AR, CA, IA, MA, NJ, NY, TX) to establish Centers for Birth Defects Research and Prevention. In September 2002 two additional states, UT and NC, were funded. One of the main activities for each Center is to conduct the NBDPS in their state (see section A.4).

Page 10:
The NBDPS is being conducted at eight locations around the country. The two new Centers will begin implementing the NBDPS in January 2003. To facilitate the compilation of the data, the interview data is sent to CDC via the Secure Data Network (SDN) using a replication feature developed in-house. The replication process enables the data to be transferred to the central storage database at the same time that the CATI program is updated. Whenever program corrections are made to the CATI, each site receives those changes when they replicate their data. This way, all of the sites are kept standardized.

Page 11:
The NBDPS is being conducted by the Centers for Birth Defects Research and Prevention (CBDRP) in seven states (AR, CA, IA, MA NJ, NY, TX) and by the DBDDD, CDC in Atlanta. The two newly funded Centers, North Carolina and Utah, will begin data collection in January 2003. All of the Centers are using the same processes for identifying eligible cases and controls, participant contact, data collection, and data processing. Collaboration among these Centers and CDC is essential for the success of the NBDPS because it allows scientists with differing expertise to work together, substantially improving the ability to better understand birth defect risk factors. Because birth defects are rare, it takes many years to accumulate enough cases of a particular defect to have the power to study risk factors for that defect. This collaborative effort will enable researchers to study the epidemiology of some rare birth defects for the first time. It may also enable researchers to identify rare exposures, such as genetic variations, that are associated with the more common birth defects.

Page 12: Consulation through other sources – same as above.

Page 15: Assurance of Confidentiality Provided to the Respondents – same as above

Page 16: Certificate of Confidentiality
The data to be covered by 301(d) confidentiality certificate protection include the interviews, clinical data, and results of testing on biological samples collected for the NBDPS. Each site

operates a state surveillance program established by law that was operational prior to the Centers study. Surveillance data already in the possession of the sites is not to be included under the certificate. The data are properly safeguarded. Hard copy documents are kept in locked file cabinets. Computer databases are password protected. Data are transferred via the Secure Data Network. Access to individually identified study information is limited to a very small number of authorized study personnel. All personnel with access to study data must sign the NBDPS Confidentiality and Data Use Oath.

2005 OMB Extension Application:

Page 7:
In 1996 CDC awarded cooperative agreements to 7 states (AR, CA, IA, MA, NJ, NY, TX) to establish Centers for Birth Defects Research and Prevention. In September 2002 two additional states, UT and NC, were funded and NJ did not receive continuation funding.

Page 10:
The NBDPS is being conducted by the Centers for Birth Defects Research and Prevention (CBDRP) in eight states (AR, CA, IA, MA, NC, NY, TX and UT) and by the DBDDD, CDC in Atlanta. All of the Centers are using the same processes for identifying eligible cases and controls, participant contact, data collection, and data processing. Collaboration among these Centers and CDC is essential for the success of the NBDPS because it allows scientists with differing expertise to work together, substantially improving the ability to better understand birth defect risk factors…

Page 12: Consulation through other sources – same as above.

Page 15: Assurance of Confidentiality Provided to the Respondents – same as above